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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 12877–12882

Double annulations of dihydroxy- and diacetoxy-dialkynylbenzenes. An efficient construction of benzodifurans

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Received 22 July 2007; revised 8 October 2007; accepted 12 October 2007
Available online 16 October 2007

Abstract—An efficient synthetic route to construct disubstituted benzodifurans from dihydroxy- or diacetoxy-dialkynylbenzenes utilizing Cs_2CO_3 or $Pd(OAc)_2/Cs_2CO_3$ promoted double annulations is described. The scope for the reaction in the presence of a catalytic amount of $Pd(OAc)_2$ is more general. In addition, it was observed that NaOH-promoted reaction of diacetoxy-dialkynylbenzenes may directly afford in THF/MeOH/H_2O at 80 °C benzodifurans through hydrolysis and double cyclization in a one-pot manner. However, in most cases, the reaction is less selective affording a mixture of the double cyclization products and monocyclization–hydrolysis products.

1. Introduction

Benzofurans and benzodifurans play a fundamental role in organic chemistry and life science because of their presence in natural products and their interesting chemical and physiological properties.[1,2] Benzofurans have been the subject of extensive studies and numerous synthetic methods have been developed.[3,4] Compared to benzofurans, reports on the synthetic methods for benzodifurans are limited:[2,5] they were usually prepared from the reaction of *p*-benzoquinone with acetoacetic acid ester,[6] aromatization of tetrahydrobenzodifuran,[2c] acid-catalyzed cyclocondensation of resorcinol with benzoin or 2-chloro-1,2-diphenyl-ethanone,[2d] intramolecular aldol-type condensation reactions of the appropriate products,[2a,7] or concomitant photocyclization and photo-Fries rearrangement reactions of dibenzoyl-dialkoxybenzene,[5] etc. On the other hand, the additions of heteroatom-centered nucleophiles to unsaturated carbon–carbon bonds are important reactions.[8] Such intramolecular additions are efficient for the construction of heterocycles.[9] For example, the metal-[3] or base-catalyzed[8] cyclization of 2-alkynylphenol or their derivatives presents an efficient synthetic method for the preparation of benzofurans.

Recently, we reported bicyclic carbopalladation,[10] double or triple Suzuki coupling reaction,[11] and triple cyclic Heck reactions[12] affording fused bicyclic or tetracyclic compounds; we also used double RCM reaction to construct bicyclic quinolizidine alkaloids[13] and tricyclic benzodipyran derivatives.[14] Here, we wish to report an efficient method for the synthesis of disubstituted benzodifurans from the double cyclization of dihydroxy- or diacetoxy-substituted dialkynylbenzenes.

2. Results and discussion

2.1. Synthesis of starting materials 4a–g

Dibromide **1** and diiodide **2**[14] were selected as the starting materials. Their Sonogashira coupling with terminal alkynes gave the corresponding products **3a**–**g** in good yields. Subsequent hydrolysis with NaOH or LiOH in THF/MeOH/H_2O gave differently substituted dihydroxydialkynylbenzenes **4a**–**g**.

2.2. Double cycloisomerization of dihydroxydialkynylbenzenes

In the beginning, the double cycloisomerization of 1,4-dihydroxy-2,5-di(1-hexynyl)benzene **4a** was investigated. The reaction of **4a** under the condition reported by Knochel[8] using Cs_2CO_3 instead of $CsOH\cdot H_2O$ as the base afforded the double cyclization product **5a** in very poor yield (entry 1, Table 1). When the solvent was changed to DMA, the yield of **5a** was improved to 60% (entry 2). By increasing the amount of Cs_2CO_3 to 2 equiv, the yield of **5a** was improved to 76% (entry 3, Condition A). With 4 equiv of Cs_2CO_3, the

Keywords: Benzodifuran; Palladium; Base; Annulation.
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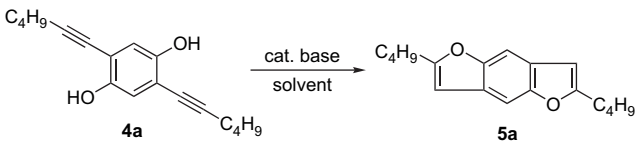
0040–4020/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tet.2007.10.051

Table 1. Double cycloisomerization of **4a** under different reaction conditions



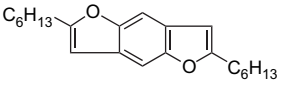
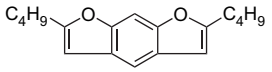
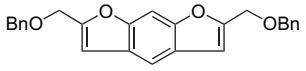
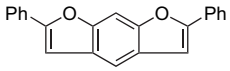
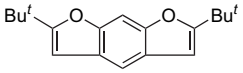
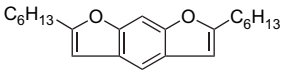
Entry	Catalyst	Solvent	Base (equiv)	T (°C)	Yield of **5a** (%)
1	—	NMP	Cs_2CO_3 (1)	80	8
2	—	DMA	Cs_2CO_3 (1)	80	60
3	—	DMA	Cs_2CO_3 (2)	80	76[a]
4	—	DMA	Cs_2CO_3 (4)	80	40
5	—	DMA	KO^{t}Bu (2)	80	8
6	—	DMA	NaOH (2)	80	22
7	—	DMA	LiOH·H_2O (2)	80	14
8	—	DMA	Cs_2CO_3 (2)	60	68
9	—	DMA	Cs_2CO_3 (2)	100	75
10	—	DMF	Cs_2CO_3 (2)	80	72
11	$PdCl_2$	DMA	Cs_2CO_3 (4)	80	62
12	$Pd(PPh_3)_2Cl_2$	DMA	Cs_2CO_3 (4)	80	62
13	$Pd(OAc)_2$	DMA	Cs_2CO_3 (4)	80	77[b]

[a] Defined as Condition A.
[b] Defined as Condition B.

yield of **5a** dropped to 40% (entry 4). Other bases, such as KO^{t}Bu, NaOH, or LiOH·H_2O, did not work well in DMA at 80 °C (entries 5–7). The effect of the temperature on the yield of **5a** is not obvious (entries 8,9). The reaction of **4a** under the catalysis of 5 mol % $PdCl_2$ in DMA at 80 °C in the presence of Cs_2CO_3 afforded the expected **5a** in only 62% yield (entry 11); using $PdCl_2(PPh_3)_2$ as the catalyst, the result is the same (entry 12), however, it was observed that by using $Pd(OAc)_2$ the yield of **5a** was improved to 77% (entry 13, Condition B).

Under the optimized Condition A, 1,4-dihydroxy-2,5-dialkynylbenzene **4b** was converted to **5b** in 73% yield (entry 1, Table 2). However, the yields for the double cyclization of 1,5-dihydroxy-2,4-dialkynylbenzenes **4c**–**g** were very low. It is interesting to observe that under the Condition B, the yields for **5c**,**d** and **5f**,**g** are obviously higher (entries 2, 3, 5, and 6). The product **5e** was formed only in trace amount under both conditions probably due to the instability

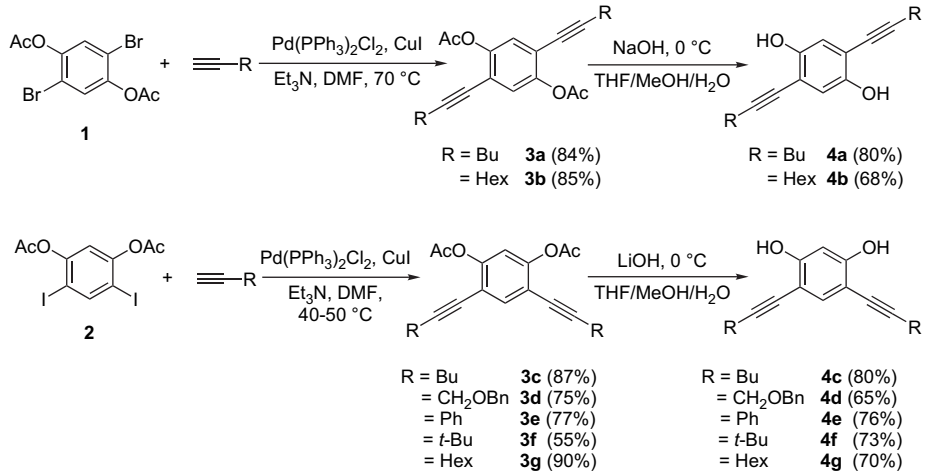
Table 2. Cycloisomerization of **4** to form disubstituted benzodifurans

Entry	Substrate	Product	Yield of **5** (%)	
			Condition A	Condition B
1	**4b**	 **5b**	73	73
2	**4c**	 **5c**	16	63
3	**4d**	 **5d**	22	35
4	**4e**	 **5e**	Trace	Trace
5	**4f**	 **5f**	12	44[b]
6	**4g**	 **5g**	34[a]	50

[a] Cs_2CO_3 (4 equiv) was used.
[b] $PdCl_2$ (5 mol %) and K_2CO_3 (4 equiv) were used.

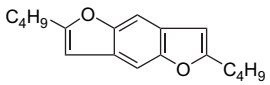
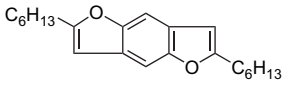
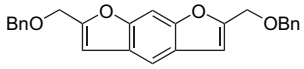
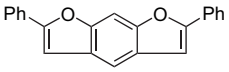
of the two phenyl-substituted furan units. The high-yielding nature of Condition B may be explained by the fact that $Pd(OAc)_2$ coordinates and subsequently activates the C–C triple bond, which may greatly facilitate the cyclization reactions.

Interestingly, further study on hydrolysis of **3a** indicated that when the reaction was conducted at 0 °C, the double hydrolysis product **4a** was formed (Scheme 1). However, when the reaction was conducted at 80 °C, sequential hydrolysis–double cyclization product **5a** was formed in good yield



Scheme 1.

Table 3. Sequential hydrolysis–double cyclization of **3** to form disubstituted benzodifurans

Entry	Substrate	Product	Yield[a] (%)
1	**3a**	 **5a**	62
2	**3b**	 **5b**	72
3	**3d**	 **5d**	34
4	**3e**	 **5e**	Trace

[a] The reaction was conducted in THF/MeOH/H_2O at 80 °C using 6 equiv of NaOH.

(entry 1, Table 3). The diacetates **3b** and **3d** may be converted to the corresponding benzodifurans **5b** and **5d** smoothly (entries 2 and 3). Product **5e** was still formed in only trace amount under this reaction condition (entry 4).

To our surprise, in the reaction of 1,5-diacetoxy-2,4-di(1-alkynyl)benzene **3c**, the desired double cyclization product **5c** was formed in 66% yield, in addition, the monocyclization–hydrolysis product benzofuran **6c** was also isolated in 16% yield. Similarly, substrate **3g** was converted to benzodifuran **5g** and benzofuran **6g** in 34 and 20% yields, respectively.[15] However, the reaction of substrate **3f** afforded monocyclization product benzofuran **6f** in 31% yield as the only product.

3. Conclusion

In summary, we have developed a convenient synthesis of disubstituted benzodifurans in moderate to good yields by using a $Pd(OAc)_2$-catalyzed double cyclization of dihydroxybis(alkyl-substituted 1-alkynyl)benzenes and a one-pot NaOH-mediated hydrolysis and double cyclization of diacetoxybis(alkyl-substituted 1-alkynyl)benzenes. However, the NaOH-mediated reaction of 1,5-diacetoxy-2,4-bis(alkyl-substituted 1-alkynyl)benzenes afforded a mixture of the double cyclization products and monocyclization–hydrolysis products in many cases. Further study in this area is being conducted in our laboratory.

4. Experimental

4.1. Synthesis of starting materials

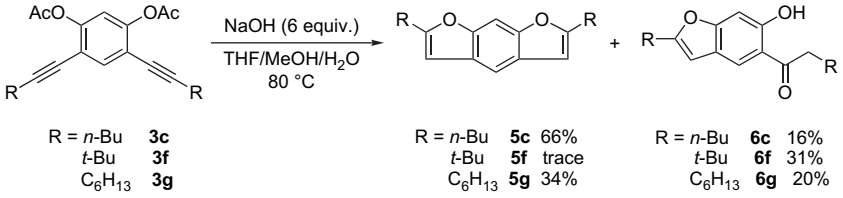
The starting materials **1**, **2**, **3a**, **3c**, **3d**, **4a**, **4c**, and **4d** were prepared according to the literature procedures.[14]

4.1.1. 2,5-Di(oct-1′-ynyl)-1,4-diacetoxybenzene (3b). Typical Procedure A. To a flame-dried reaction tube were added sequentially **1** (500 mg, 1.42 mmol), $PdCl_2(PPh_3)_2$ (48 mg, 0.07 mmol), CuI (28 mg, 0.15 mmol), DMF (2 mL), Et_3N (2 mL), and 1-octyne (625 mg, 5.68 mmol) under Ar. After being stirred at 80 °C under Ar for 11 h, the reaction mixture was quenched with water, extracted with Et_2O, washed with brine, and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ethyl acetate=20:1) gave the coupling product **3b** (498 mg, 85%) as a white solid, mp: 61–62 °C (petroleum ether/ethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 2H), 2.38 (t, J=6.9 Hz, 4H), 2.28 (s, 6H), 1.60–1.48 (m, 4H), 1.46–1.22 (m, 12H), 0.88 (t, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 148.6, 126.1, 118.3, 97.5, 74.7, 31.2, 28.4, 22.4, 20.6, 19.4, 13.9; MS (MALDI) *m/z*: 433.4 ($M+Na^+$); IR (neat) ν (cm^{-1}): 2933, 2859, 2232, 1774, 1496, 1196, 1156; Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.06, H, 8.35; Found: C, 76.00, H, 8.48.

The following compounds were prepared according to Procedure A.

4.1.2. 2,4-Bis(phenylethynyl)-1,5-diacetoxybenzene (3e). The reaction of **2** (400 mg, 0.9 mmol), Et_3N (3 mL), phenylacetylene (550 mg, 5.39 mmol), $PdCl_2(PPh_3)_2$ (13 mg, 0.019 mmol), and CuI (7 mg, 0.037 mmol) in DMF (3 mL) afforded the coupling product **3e** (275 mg, 77%) as a white solid after being stirred at 50 °C for 21.5 h under Ar, mp: 123–124 °C (petroleum ether/ethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.51–7.46 (m, 4H), 7.39–7.35 (m, 6H), 7.04 (s, 1H), 2.37 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 151.4, 136.4, 131.5, 128.7, 128.4, 122.5, 117.1, 115.5, 94.6, 82.9, 20.8; MS (EI) *m/z* (%): 394 (M^+, 3.5), 310 (100.0); IR (neat) ν (cm^{-1}): 2222, 1774, 1502, 1369, 1189, 1146; Anal. Calcd for $C_{26}H_{18}O_4$: C, 79.17, H, 4.60; Found: C, 79.47, H, 4.65.

4.1.3. 2,4-Bis(*tert*-butylethynyl)-1,5-diacetoxybenzene (3f). The reaction of **2** (2 g, 4.5 mmol), Et_3N (5 mL), *tert*-butylethyne (2.2 g, 26.8 mmol), $PdCl_2(PPh_3)_2$ (63 mg, 0.09 mmol), and CuI (34 mg, 0.18 mmol) in DMF (5 mL) afforded the coupling product **3f** (0.879 g, 55%) as a white



R = *n*-Bu **3c**; *t*-Bu **3f**; C_6H_{13} **3g**

R = *n*-Bu **5c** 66%; *t*-Bu **5f** trace; C_6H_{13} **5g** 34%

R = *n*-Bu **6c** 16%; *t*-Bu **6f** 31%; C_6H_{13} **6g** 20%

solid after being stirred at 40 °C for 12 h under Ar, mp: 108–109 °C (petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.84 (s, 1H), 2.28 (s, 6H), 1.27 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 150.7, 136.3, 116.4, 116.0, 103.7, 72.8, 30.7, 28.0, 20.6; MS (EI) *m/z* (%): 354 (4.0), 270 (100); IR (neat) ν (cm^{-1}): 2969, 2231, 1775, 1495, 1367, 1190, 1106; Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55, H, 7.39; Found: C, 74.54, H, 7.36.

4.1.4. 2,4-Di(oct-1′-ynyl)-1,5-diacetoxybenzene (3g). The reaction of **2** (500 mg, 1.13 mmol), Et_3N (2 mL), 1-octyne (495 mg, 4.5 mmol), $PdCl_2(PPh_3)_2$ (32 mg, 0.046 mmol), and CuI (17 mg, 0.09 mmol) in DMF (2 mL) afforded the coupling product **3g** (412 mg, 90%) as an oil after being stirred at 40 °C for 3.5 h under Ar. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.86 (s, 1H), 2.38 (t, J=6.9 Hz, 4H), 2.29 (s, 6H), 1.61–1.48 (m, 4H), 1.46–1.21 (m, 12H), 0.89 (t, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 150.7, 136.6, 116.6, 116.0, 95.8, 74.2, 31.3, 28.5, 28.4, 22.5, 20.7, 19.4, 14.0; MS (EI) *m/z* (%): 410 (M^+, 12.6), 326 (100); IR (neat) ν (cm^{-1}): 2932, 2859, 2233, 1776, 1493, 1190, 1128; HRMS Calcd for $C_{26}H_{34}O_4Na^+$ ($M+Na^+$): 433.2349; Found: 433.2357.

4.1.5. 2,5-Di (oct-1′-ynyl)-1,4-dihydroxybenzene (4b). Typical Procedure B. To the solution of **3b** (340 mg, 0.82 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 20 mL) was added NaOH (140 mg, 3.5 mmol) at 0 °C. The resulting solution was stirred at this temperature for 30 min as monitored by TLC. The mixture was neutralized with aq HCl, extracted with ethyl ether, washed with brine, and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ethyl acetate=10:1) gave **4b** (184 mg, 68%) as a white solid, mp: 87–88 °C (petroleum ether/ethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H), 5.42 (s, 2H), 2.46 (t, J=6.9 Hz, 4H), 1.64–1.55 (m, 4H), 1.47–1.26 (m, 12H), 0.90 (t, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 116.2, 111.2, 99.1, 74.5, 31.3, 28.59, 28.55, 22.5, 19.6, 14.0; MS (EI) *m/z* (%): 326 (M^+, 100); IR (neat) ν (cm^{-1}): 3309, 2928, 2859, 2225, 1422, 1193; Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94, H, 9.26; Found: C, 81.14, H, 9.27.

The following compounds were prepared according to Procedure B.

4.1.6. 2,4-Bis(phenylethynyl)-1,5-dihydroxybenzene (4e). The reaction of **3e** (278 mg, 0.71 mmol) and LiOH (68 mg, 2.83 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 10 mL) afforded the product **4e** (198 mg, 91%) as a brown solid after being stirred at 0 °C for 35 min, mp: 114–115 °C (petroleum ether/ethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.51 (m, 5H), 7.43–7.36 (m, 6H), 6.65 (s, 1H), 6.07 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 134.6, 131.5, 128.7, 128.5, 122.3, 102.9, 101.4, 95.5, 82.0; MS (EI) *m/z* (%): 310 (100.0); IR (neat) ν (cm^{-1}): 3497, 1626, 1595, 1501, 1271; Anal. Calcd for $C_{22}H_{14}O_2$: C, 85.14, H, 4.55; Found: C, 85.15, H, 4.65.

4.1.7. 2,4-Di(*tert*-butylethynyl)-1,5-dihydroxybenzene (4f). The reaction of **3f** (220 mg, 0.62 mmol) and LiOH (59 mg, 2.46 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 10 mL) afforded the product **4f** (122 mg, 73%) as a white solid after being stirred at 0 °C for 30 min, mp: 74–75 °C (petroleum ether/ethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.52 (s, 1H), 5.83 (br s, 2H), 1.32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 133.9, 105.0, 102.9, 100.4, 72.0, 31.1, 28.3; MS (EI) *m/z* (%): 270 (100.0); IR (neat) ν (cm^{-1}): 3499, 2969, 2928, 1631, 1496, 1272; Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96, H, 8.20; Found: C, 80.02, H, 8.15.

4.1.8. 2,4-Di(oct-1′-ynyl)-1,5-dihydroxybenzene (4g). The reaction of **3g** (300 mg, 0.73 mmol) and $LiOH\cdot H_2O$ (132 mg, 3.14 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 20 mL) afforded the product **4g** (186 mg, 78%) as an oil after being stirred at 0 °C for 30 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.52 (s, 1H), 5.92 (br s, 2H), 2.42 (t, J=6.9 Hz, 4H), 1.64–1.52 (m, 4H), 1.50–1.22 (m, 12H), 0.90 (t, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 133.9, 103.0, 100.6, 96.7, 73.6, 31.3, 28.7, 28.6, 22.5, 19.5, 14.0; MS (EI) *m/z* (%): 326 (M^+, 100); IR (neat) ν (cm^{-1}): 3497, 2930, 2858, 1629, 1586, 1492, 1354, 1272, 1146; HRMS Calcd for $C_{22}H_{30}O_2$: 326.2246; Found: 326.2253.

4.2. Double cycloisomerization of 4

4.2.1. 2,6-Dibutylbenzo[1,2-*b*:4,5-*b*′]difuran (5a). Typical Procedure C: Condition A. To a reaction tube were added sequentially **4a** (50 mg, 0.19 mmol), Cs_2CO_3 (120 mg, 0.37 mmol), and DMA (2 mL). The reaction mixture was stirred for 2.5 h at 80 °C, quenched with water, extracted with ether, and washed with brine. Evaporation and flash column chromatography on silica gel (petroleum ether) gave **5a** (38 mg, 76%) as a white solid, mp: 55–56 °C (petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 2H), 6.40 (s, 2H), 2.77 (t, J=7.8 Hz, 4H), 1.80–1.70 (m, 4H), 1.50–1.40 (m, 4H), 0.97 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 151.6, 125.8, 101.9, 100.6, 29.7, 28.3, 22.3, 13.8; MS (EI) *m/z* (%): 270 (50.3), 227 (100.0); IR (neat) ν (cm^{-1}): 2960, 2932, 1606, 1437; Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96, H, 8.20; Found: C, 80.11, H, 8.18.

The following compounds were prepared according to Condition A.

4.2.2. 2,6-Dioctylbenzo[1,2-*b*:4,5-*b*′]difuran (5b). The reaction of **4b** (62 mg, 0.19 mmol) and Cs_2CO_3 (126 mg, 0.39 mmol) in DMA (2 mL) afforded the product **5b** (19 mg, 31%) as a white solid after being stirred at 80 °C for 5.5 h, mp: 62–63 °C (petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 2H), 6.40 (s, 2H), 2.76 (t, J=7.8 Hz, 4H), 1.80–1.70 (m, 4H), 1.50–1.25 (m, 12H), 0.89 (t, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 151.6, 125.8, 101.9, 100.6, 31.6, 28.9, 28.7, 27.6, 22.6, 14.1; MS (EI) *m/z* (%): 326 (M^+, 52.4), 255 (100); IR (neat) ν (cm^{-1}): 2930, 2848, 1603, 1470, 1437; Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94, H, 9.26; Found: C, 80.90, H, 9.41.

4.2.3. 2,6-Dibutylbenzo[1,2-*b*:5,4-*b*′]difuran (5c). The reaction of **4c** (50 mg, 0.19 mmol) and Cs_2CO_3 (120 mg, 0.37 mmol) in DMA (2 mL) afforded the product **5c** (8 mg, 16%) as a white solid after being stirred at 80 °C for 11 h, mp: 38 °C (petroleum ether). ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.46 (s, 1H), 6.40 (s, 2H), 2.79 (t, J=7.2 Hz, 4H), 1.82–1.72 (m, 4H), 1.50–1.42 (m, 4H), 0.99 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 152.3, 125.2, 109.1, 101.4, 93.5, 29.7, 28.3, 22.3, 13.8; MS (EI) *m/z* (%): 270 (M^+, 34.5), 227 (100.0); IR (neat) ν (cm^{-1}): 2957, 2931, 1604, 1441; Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96, H, 8.20; Found: C, 80.36, H, 8.39.

4.2.4. 2,6-Bis(benzyloxymethyl)benzo[1,2-*b*:5,4-*b*′]difuran (5d). The reaction of **4d** (50 mg, 0.13 mmol) and Cs_2CO_3 (82 mg, 0.25 mmol) in DMA (2 mL) afforded the product **5d** (11 mg, 22%) as a white solid after being stirred for 16 h at 80 °C, mp: 72–73 °C (petroleum ether/ethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.61 (s, 1H), 7.40–7.31 (m, 10H), 6.75 (s, 2H), 4.65 (s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 153.6, 137.6, 128.5, 128.0, 127.8, 124.8, 111.3, 105.7, 94.6, 72.3, 64.5; MS (EI) *m/z* (%): 398 (M^+, 3.3), 44 (100.0); IR (neat) ν (cm^{-1}): 2856, 1608, 1454, 1438, 1351; Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37, H, 5.57; Found: C, 78.45, H, 5.62.

4.2.5. 2,6-Di(*tert*-butyl)benzo[1,2-*b*:5,4-*b*′]difuran (5f). The reaction of **4f** (50 mg, 0.19 mmol) and Cs_2CO_3 (120 mg, 0.37 mmol) in DMA (2 mL) afforded the product **5f** (6 mg, 12%) as a white solid after being stirred at 80 °C for 11 h, mp: 110–112 °C (petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.45 (s, 1H), 6.35 (s, 2H), 1.38 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 152.4, 125.1, 109.5, 98.6, 93.6, 33.0, 28.8; MS (EI) *m/z* (%): 270 (M^+, 31.6), 255(100); IR (neat) ν (cm^{-1}): 2960, 2868, 1590, 1440, 1107; Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96, H, 8.20; Found: C, 80.01, H, 8.49.

4.2.6. 2,6-Dioctylbenzo[1,2-*b*:5,4-*b*′]difuran (5g). The reaction of **4g** (50 mg, 0.15 mmol) and Cs_2CO_3 (200 mg, 0.61 mmol) in DMA (2 mL) afforded the product **5g** (17 mg, 34%) as a white solid after being stirred at 80 °C for 16.5 h, mp: 43–44 °C (petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.46 (s, 1H), 6.40 (s, 2H), 2.77 (t, J=7.5 Hz, 4H), 1.82–1.70 (m, 4H), 1.47–1.30 (m, 12H), 0.92 (t, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 152.3, 125.2, 109.1, 101.4, 93.5, 31.6, 28.9, 28.6, 27.6, 22.6, 14.1; MS (EI) *m/z* (%): 326 (M^+, 50.2), 255 (100); IR (neat) ν (cm^{-1}): 2929, 2858, 1604, 1441, 1131; Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94, H, 9.26; Found: C, 81.02, H, 9.45.

4.2.7. 2,6-Bisbutylbenzo[1,2-*b*:4,5-*b*′]difuran (5a). Typical Procedure D: Condition B. To a solution of **4a** (61 mg, 0.22 mmol) in DMA (2.5 mL) were added $Pd(OAc)_2$ (3 mg, 0.013 mmol) and Cs_2CO_3 (290 mg, 0.89 mmol) in open air. The reaction mixture was stirred for 9 h at 80 °C, quenched with water, neutralized with aq HCl, extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether) gave **5a** (47 mg, 77%) as a white solid.

The following compounds were prepared according to Procedure D.

4.2.8. 2,6-Bisoctylbenzo[1,2-*b*:4,5-*b*′]difuran (5b). The reaction of **4b** (52 mg, 0.16 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol) and Cs_2CO_3 (200 mg, 0.61 mmol) in DMA (2 mL) afforded **5b** (38 mg, 73%) as a white solid after being stirred at 80 °C for 9 h.

4.2.9. 2,6-Dibutylbenzo[1,2-*b*:5,4-*b*′]difuran (5c). The reaction of **4c** (80 mg, 0.30 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol), and Cs_2CO_3 (387 mg, 1.19 mmol) in DMA (2.5 mL) afforded **5c** (50 mg, 63%) as a white solid after being stirred at 80 °C for 3 h.

4.2.10. 2,6-Bis(benzyloxymethyl)benzo[1,2-*b*:5,4-*b*′]difuran (5d). The reaction of **4d** (120 mg, 0.3 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol), and Cs_2CO_3 (391 mg, 1.2 mmol) in DMA (3 mL) afforded the product **5d** (42 mg, 35%) as a white solid after being stirred at 60 °C for 18 h.

4.2.11. 2,6-Di(*tert*-butyl)benzo[1,2-*b*:5,4-*b*′]difuran (5f). The reaction of **4f** (64 mg, 0.24 mmol), $PdCl_2$ (2 mg, 0.011 mmol), and K_2CO_3 (121 mg, 0.88 mmol) in DMA (2 mL) afforded the product **5f** (28 mg, 44%) as a white solid after being stirred at 80 °C for 5 h.

4.2.12. 2,6-Dioctylbenzo[1,2-*b*:5,4-*b*′]difuran (5g). The reaction of **4g** (60 mg, 0.18 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and Cs_2CO_3 (240 mg, 0.74 mmol) in DMA (2 mL) afforded the product **5g** (30 mg, 50%) as a white solid after being stirred at 80 °C for 16.5 h.

4.3. Hydrolysis and double cyclization of 3

4.3.1. 2,6-Dibutylbenzo[1,2-*b*:4,5-*b*′]difuran (5a). Typical Procedure E. To the solution of **3a** (80 mg, 0.23 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 2 mL) was added NaOH (62 mg, 1.55 mmol). After being stirred at 80 °C for 4 h, the reaction mixture was quenched with water, extracted with Et_2O, washed with brine, and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether) gave the product **5a** (38 mg, 62%) as a white solid.

The following compounds were prepared according to Procedure E.

4.3.2. 2,6-Dioctylbenzo[1,2-*b*:4,5-*b*′]difuran (5b). The reaction of **3b** (80 mg, 0.20 mmol) and NaOH (50 mg, 1.25 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 3 mL) afforded the product **5b** (46 mg, 72%) as a white solid after being stirred at 80 °C for 17.5 h.

4.3.3. 2,6-Dibutylbenzo[1,2-*b*:5,4-*b*′]difuran (5c). The reaction of **3c** (85 mg, 0.24 mmol) and NaOH (55 mg, 1.38 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 3 mL) afforded the product **5c** (43 mg, 66%) as a white solid and **6c** (11 mg, 16%) as an oil after being stirred at 80 °C for 11 h. Compound **6c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.60 (s, 1H), 7.87 (s, 1H), 6.94 (s, 1H), 6.29 (s, 1H), 3.02 (t, J=7.5 Hz, 2H), 2.72 (t, J=7.5 Hz, 2H), 1.78–1.62 (m, 4H), 1.48–1.26 (m, 6H), 1.00–0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 160.70, 160.66, 159.3, 121.8, 121.7, 116.0, 101.4, 99.4, 38.4, 31.5, 29.5, 28.0, 24.6, 22.5, 22.2, 14.0, 13.8; MS (EI) *m/z* (%): 288 (M^+, 58.0), 217 (100); IR (neat) ν (cm^{-1}): 2957, 2929, 2860, 1643, 1610, 1463; HRMS Calcd for $C_{18}H_{24}O_3$: 288.1725; Found: 288.1721.

4.3.4. 2,6-Bis(benzyloxymethyl)benzo[1,2-*b*:5,4-*b*′]difuran (5d). The reaction of **3d** (90 mg, 0.19 mmol) and NaOH (50 mg, 1.25 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 2 mL) afforded the product **5d** (25 mg, 34%) as a white solid after being stirred at 80 °C for 11 h.

4.3.5. 1-(2-*tert*-Butyl-6-hydroxybenzofuran-5-yl)-3,3-dimethylbutan-1-one (6f). The reaction of **3f** (80 mg, 0.23 mmol) and NaOH (70 mg, 1.75 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 2 mL) afforded the product **6f** (20 mg, 33%) as an oil after being stirred at 80 °C for 17 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.89 (s, 1H), 7.88 (s, 1H), 6.95 (s, 1H), 6.27 (s, 1H), 2.88 (s, 2H), 1.35 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 168.3, 161.1, 159.4, 123.0, 121.4, 117.3, 99.4, 98.7, 49.7, 32.9, 32.0, 30.3, 28.6; MS (ESI) *m*/*z* (%): 289.3 ($M+H^+$); IR (neat) ν (cm^{-1}): 2962, 1638, 1605; HRMS Calcd for $C_{18}H_{24}O_3$: 288.1725; Found: 288.1732.

4.3.6. 2,6-Dioctylbenzo[1,2-*b*:5,4-*b*′]difuran (5g). The reaction of **3g** (78 mg, 0.19 mmol) and NaOH (53 mg, 1.33 mmol) in a mixed solvent (MeOH/THF/H_2O=1:1:1, 3 mL) afforded the product **5g** (21 mg, 34%) as a white solid and **6g** (13 mg, 20%) as an oil after being stirred at 80 °C for 9 h. Compound **6g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.61 (s, 1H), 7.87 (s, 1H), 6.95 (s, 1H), 6.29 (s, 1H), 3.02 (t, *J*=7.5 Hz, 2H), 2.71 (t, *J*=7.5 Hz, 2H), 1.79–1.68 (m, 4H), 1.46–1.18 (m, 14H), 0.89 (t, *J*=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 160.70, 160.68, 159.3, 121.8, 121.7, 116.0, 101.4, 99.4, 38.5, 31.7, 31.5, 29.3, 29.1, 28.8, 28.3, 27.4, 24.9, 22.6, 22.5, 14.09, 14.06; MS (EI) *m*/*z* (%): 344 (M^+, 57.1), 245 (100); IR (neat) ν (cm^{-1}): 2927, 2855, 1642, 1605, 1460, 1132; HRMS Calcd for $C_{22}H_{32}O_3$: 344.2351; Found: 344.2354.

Acknowledgements

Financial support from the Major State Basic Research Development Program (Grant No. 2006CB806105), National NSF of China (Nos. 20172060, 200423001, and 20121202), and Shanghai Municipal Committee of Science and Technology is greatly appreciated.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.051.

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